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The proportion of second cancers attributable to radiotherapy treatment in adults: a prospective cohort study in the US SEER cancer registries

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Abstract

Background—As cancer survival improves, the long-term risks from treatments including the risk of developing a second cancer after radiotherapy become more important. The proportion of second cancers that may be related to radiotherapy is unknown.

Methods—We used the U.S. Surveillance, Epidemiology and End Results cancer registries to conduct a systematic analysis of 15 cancer sites that are treated routinely with radiotherapy. Relative risks (RR) for patients receiving radiotherapy versus patients not receiving radiotherapy were estimated using Poisson regression adjusted for age, stage and other potential confounders.

Findings—The cohort included 647,672 five-year adult survivors followed-up for an average of 7 additional years; 60,271 (9%) developed a second solid cancer. For each of the first cancer sites the RR of developing a second cancer associated with radiotherapy exceeded one, and varied from 1.08 (95% CI:0.79–1.46) after eye/orbit cancers to 1.43 (95% CI:1.13–1.84) after testicular cancer. In general the RR was highest for organs likely to have received >5Gy, decreased with increasing age at diagnosis and increased with time since diagnosis. We estimated a total of 3266 (95% CI: 2862–3670) excess second solid cancers that could be related to radiation; 8% (95% CI:7%–9%) of the total in all radiotherapy patients (1+yr survivors) and 5 excess cancers/1,000 patients treated with radiotherapy by 15 years after diagnosis. Approximately half (54%) the excess cancers were in organs likely to have received >5Gy.

Interpretation—A relatively small proportion of second cancers are related to radiotherapy in adults, suggesting that most are due to other factors, such as lifestyle or genetics.

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Introduction

Radiotherapy treatment decreases the risk of cancer recurrence, promotes tumor control and improves survival.¹ However, with improved survival, the long-term risks from radiotherapy, including the risk of developing a second cancer, become a more important consideration. Subsequent malignancies in cancer survivors now constitute 18% of all cancer diagnoses in the U.S Surveillance, Epidemiology & End Results (SEER) cancer registries making them the 3rd most common cancer diagnosis.² Compared to the general population cancer survivors have about a 14% higher rate of cancer.³ These increased risks are likely the result of a combination of shared lifestyle and genetic factors, as well as the treatment for the first cancer. Although numerous studies have demonstrated an association between radiotherapy and the risk of developing a second cancer, the proportion of second cancers that might be related to radiotherapy is not known. In two recent studies we used the SEER cancer registries to develop some of the first estimates of the attributable risk for specific first cancers and concluded that about 5–6% of second solid cancers after breast cancer⁴ and 11% after endometrial cancer⁵ may be related to radiotherapy. In the current study we extend this analysis to conduct a comprehensive and systematic analysis of all first solid cancer sites in adults that are routinely treated with radiotherapy in the U.S. SEER registries. The large population covered by these registries, combined with more than three decades of follow-up, enables long-term detailed evaluation of the patterns of risk after radiotherapy.

Methods

Population and follow-up

The cohort was composed of adult patients (age 20+) who were diagnosed with a first primary invasive solid cancer reported in the SEER nine registries between January 1 1973 and December 31 2002.² We included 15 solid cancer sites that are routinely treated with radiotherapy; defined as >20% patients received radiation treatment as part of their first treatment course and with >200 second cancers to enable stable risk estimation. The fifteen first cancer sites were: oral/pharynx, salivary gland, rectum, anus, larynx, lung, soft tissue, breast, cervix, endometrial, prostate, testes, eye/orbit, brain/CNS and thyroid. Because, in general, there is at least a five year lag period between radiation exposure and solid cancer inunction⁶ we excluded patients who survived less than five years from the analysis. This restriction also ensured that we eliminated any surveillance bias that might result if patients who received radiotherapy were monitored more intensively than other patients in the first five years. The follow-up time (person-years at risk) for second cancers for each individual began five years after the date of initial cancer diagnosis and ended at the date of diagnosis of any second malignant cancer, last known vital status, death or the end of study (December 31, 2007), whichever occurred first. Patients were censored at age 85 years as there is evidence of under ascertainment of second primary cancers after that age in SEER.³ We excluded patients with missing information on radiotherapy or stage, unless the first primary was prostate, brain or lung cancer as stage information was often unavailable for these cancers during the study period. We excluded hematological cancers from both the first and second cancer sites because of potential confounding by chemotherapy, details of which were not available. For similar reasons we also excluded non-seminoma testicular cancers and small-cell lung cancers. Finally, soft tissue sarcomas that occurred in extremities were excluded because radiotherapy for these cancers would be unlikely to result in second solid cancers.

Treatment information

SEER cancer registries collect information on the initial course of treatment. Patients were classified according to whether or not they had received radiotherapy as part of their initial cancer treatment and the type of radiotherapy given: external beam, brachytherapy or combination therapy (external beam and brachytherapy).

Classification of second cancers

In order to provide sufficient statistical power for risk estimation, the analyses were conducted for all second solid cancers combined. In addition, for the first cancer sites with at least 1000 second cancers, the typical radiation doses delivered to each second cancer site were estimated using standard radiotherapy protocols from the period of study. The distance of the second cancer site from the border of the primary radiotherapy field was then used to categorize the second cancer sites into broad groups: <3cm high-dose (>5Gy), 3–10cm medium-dose (1–5Gy) and >10cm low-dose (<1Gy).⁷ Dose groups for thyroid cancer were based on I-131 treatment assuming an administered activity of 200 mCi.^{8–10} The second cancer dose groupings for the nine eligible first cancer sites are available in Webtable 1.

Statistical analysis

Poisson regression analysis was used to estimate the relative risk (RR) (and 95% confidence intervals) in patients who received radiotherapy compared to those who did not receive radiotherapy. These risks were adjusted for potential confounding factors: stage, age at and year of first cancer diagnosis, and additionally adjusted for calendar period and attained age by using the expected number of second cancers in the general population as an offset.^{2,12} We examined effect modification of the risk associated with radiotherapy by age at first cancer diagnosis, time since initial diagnosis and calendar year of diagnosis. This analysis was restricted to the outcome of high-dose second cancer sites to maximize power to detect differences. We also conducted a sensitivity analysis where we examined the risk associated with radiotherapy in the sub-group of patients who were surgically treated for their first cancer. All analyses were conducted using EPICURE AMFIT.¹³

We estimated the number of excess second cancers related to radiotherapy by taking the number of second cancers in those treated with radiotherapy minus the number that would have occurred in these subjects if they had not received radiotherapy (estimated from the Poisson regression models). Although the analysis of excess cancers was restricted to 5+ year survivors (to eliminate potential surveillance bias in the early period of follow-up) the overarching goal of this study was to estimate the proportion of second solid cancers related radiotherapy among all cancer survivors. Therefore, we expressed this excess as a proportion of the total number of second cancers observed in all cancer survivors (defined as 1+ year survivors). We calculated the number of second cancers in 1+ year survivors using the SEER cancer registries database applying the same exclusions as defined above for the 5+ year survivors. This approach assumes that the number of radiation-related cancers in the first five years is zero.

We also estimated the excess number of cancers that occurred by 15 years and divided this number by the total number of patients who received radiotherapy (again using 1+ year survivors). This provided an estimate of the cumulative excess risk by 15 years after diagnosis. The overall excess and attributable risks were then estimated by summing across all 15 first cancer sites.

Role of Funding Source: The study sponsors did not have any role in the design of the study; collection, analysis, and interpretation of the data; writing of the report; or in the decision to

submit for publication. AB and REC had access to the raw data. AB has full access to all of the data and the final responsibility to submit for publication.

The study did not require ethics committee approval as the data are publically available.

Results

After the exclusions the cohort included 647,672 five-year adult cancer survivors who were followed for an average of 12 years (SD=4.5, range 5–24). The proportion of patients who received radiotherapy as part of their initial cancer treatment varied from 23% for (non-small cell) lung cancer to 79% for testicular cancer (seminomas) (Table 1). Patterns of radiotherapy varied across the first cancer sites but, in general, receipt of radiotherapy was slightly less common in the oldest patients (age 75–79 years) and for localized stage disease, and was more common in recent calendar time periods. The main exceptions to these patterns were cervical and endometrial cancer where radiotherapy was more common in older women and for more advanced stage disease and was less common in recent time periods.

During the follow-up period (1978–2007) a total of 60,271 (9%) of the five-year survivors developed a second solid cancer. For each of the first cancer sites the relative risk of developing a second solid cancer associated with radiotherapy was greater than one, and for the majority of first cancer sites the increased risk was statistically significant (Figure 1). The adjusted relative risk for radiotherapy varied from 1.08 (95%CI:0.79–1.46) after eye/orbit cancers to 1.43 (95%CI:1.13–1.84) after testicular cancer (seminomas). Adjustment for stage at diagnosis, age at diagnosis, year of diagnosis of the first cancer had a modest impact on the relative risk estimates, generally reducing the risks slightly (Webtable 1). Restricting the cohort to patients treated with surgery did not change the relative risks by more than 10% except for eye/orbit cancers, which were based on very small numbers (Webtable 2). When we examined the relative risks associated with radiotherapy treatment for the group of second cancers that are related to smoking we found that these risks were generally higher than the risks for second cancers not related to smoking, possibly indicating confounding by smoking (Webtable 3).

For six of the nine first cancer sites for which we conducted grouped dose-response analyses the relative risk for radiotherapy was higher for the group of high-dose second cancer sites (>5Gy) compared to sites estimated to have received moderate or low radiation doses from the primary field (Figure 2). The RR for the high-dose second cancer sites varied from 1.03 (95%CI:0.71–1.47) after thyroid cancer to 1.78 (95%CI:1.42–2.22) after cervical cancer. For breast, endometrial and prostate cancer there was a highly significant trend across the dose-groups ($p<0.0001$). There was also a suggestion of a decreasing trend for laryngeal ($p=0.13$) and cervical cancer ($p=0.082$). For the remaining sites the patterns of risk were less consistent. Results for each individual second cancer site and each dose-group are available in Webtable 1.

We examined effect modification by age and year of diagnosis and time since diagnosis for high-dose second solid cancers. The relative risks associated with radiotherapy decreased significantly with increasing age at diagnosis for second cancers after breast ($p<0.0001$), cervical ($p=0.00068$), endometrial ($p=0.036$) and prostate cancer ($p=0.00070$) (Table 2). The RRs increased significantly with increasing time since diagnosis after cancer of the lung ($p=0.0079$), breast ($p=0.0013$), cervix ($p=0.0032$), endometrium ($p<0.0001$) and prostate ($p=0.0031$) (Table 3). The RRs decreased with increasing calendar year of diagnosis for second cancers after breast cancer ($p<0.001$) and endometrial cancer ($p=0.064$), but for the

other sites there were no clear patterns (Webtable 4). As all these time variables are likely to be correlated, these patterns should be interpreted with some caution.

In total there were an estimated 3266 (95%CI: 2862–3670) excess second solid cancers that could be related to radiotherapy in these 5-year survivors (Table 4). Assuming no excess radiation-related solid cancers would occur in the first 5 years of follow-up, we estimated that 8% (95%CI: 7%–9%) of the total 42,302 second solid cancers diagnosed in 1+ year survivors could be attributed to radiotherapy. This figure varied from 4% (95%CI: –11%–20%) after eye/orbit cancers to 24% (95%CI: 9%–37%) after testicular cancer (seminomas). Overall, for every 1,000 patients treated with radiotherapy there were an estimated 3 excess cancers by 10 years after first cancer diagnosis, by 15 years this figure was 5 excess cancers (data not shown). Over half the observed (56%, n=23,742) and the excess cancers (55%, n=1791) occurred in breast and prostate cancer survivors.

In the nine first cancer sites for which we assessed risk according to broad dose-groups about half of the estimated excess radiation-related cancers (54%, n=1541) were in the high-dose group (>5Gy) compared to 28% (n=10,535) of observed second cancers (data not shown). In contrast 29% (n=839) of the excess cancers were in the low-dose group compared to 49% (n=18,601) of the observed second cancers. To assess the potential impact of bias in the low-dose group we also estimated the attributable risk for these nine first cancers excluding the low-dose group excess, this decreased the estimate from 7% (95%CI: 6%–8%) to 5% (95%CI: 4%–6%). For the high-dose cancer sites, 37% (n=566) of the excess cases occurred among patients irradiated at ages 45–59 years and 51% (n=812) after treatment aged 60–74 years.

Discussion

To our knowledge, this is the first study to estimate the proportion of second cancers overall in adult cancer survivors that might be related to radiotherapy treatment. Our results suggest that about 8% (95%CI: 7%–9%) of second solid cancers may be related to the radiotherapy treatment for the first cancer. This figure varied according to first cancer site, from 4% for eye/orbit cancers to 24% for testicular cancer. Higher attributable risks were most likely due to younger age at treatment, larger treatment fields and the organs located in those fields. In general the relative risks decreased with increasing age, and increased with increasing time since diagnosis. By 15 years after diagnosis there were an estimated 5 excess cancers per 1000 patients treated with radiotherapy.

Although there have been a large number of studies of second cancers after radiotherapy treatment, few have assessed the attributable risk or cumulative absolute risk. We previously estimated that 5–6% of second solid cancers after breast cancer were related to radiotherapy in the SEER cancer registries.⁴ Using published results from the pooled analysis of randomized radiotherapy trials for breast cancer we estimated a similar attributable risk (8%), which suggests that our estimate was not subject to strong confounding by indication.¹⁴ In an earlier analysis of cervical cancer patients using cancer registries Boice et al estimated an attributable risk of 5%,¹⁵ which is considerably smaller than the estimate of 17% (95%CI: 10%–23%) in the current study. One possible reason for this difference was use of the general population as the comparison group in the previous study, due to the small number of patients who did not receive radiotherapy during that study's time period. Also only cancers that were considered to be radiation-inducible were included in the excess, for example rectal cancers were excluded in the previous study but they are now considered to be radiation-inducible⁶ and were included here. In a previous study of prostate cancer radiotherapy using SEER registries Brenner et al estimated that there were 3 excess cancers/

1000 patients in all survivors,¹⁶ which is similar in magnitude to our overall estimate of 5 cancers/1000.

A number of previous studies have estimated the dose-response relationship for specific second solid cancers after radiotherapy based on individual treatment records. One such study of cervical cancer treatment found a positive dose-response relationship for second cancers of the bladder, rectum, bone, stomach and all female genital cancers combined after radiotherapy for cervical cancer.¹⁷ In breast cancer patients dose-response relationships have also been observed for lung, bone, connective tissue and contralateral breast cancers after radiotherapy,^{18–22} and for stomach cancer after testicular cancer and Hodgkin lymphoma.²³ Although the site-specific risks were not the focus of the current study, the patterns of the risks were generally consistent with these previous reports (Webtable 1). There is also a large body of evidence from registry based studies with more limited details on the radiotherapy treatment (yes/no and external beam/brachytherapy) and hospital series. These studies include a number of analyses of SEER registries that focused on a single first cancer. Our results were broadly consistent with those previous reports, which found that those treated with radiotherapy have a small (RR=1.1–1.4) increased risk of a second cancer overall compared to those who did not receive radiotherapy (Webtable 5).^{4,5,24–37}

The strengths of the current study include the systematic approach used to assess all first cancer sites, which enabled comparisons of risks across first cancer sites and examination of common patterns of risk. The large sample size and long-term follow-up are also key strengths of the SEER registries for assessing the late-effects of radiotherapy, along with comprehensive coding rules for second cancers, which have changed minimally over time. We assessed the plausibility that the observed relationships were causal by examining the dose-response across groups of second cancer sites and the relationship with age at exposure and latency. Mostly these followed the expected patterns, i.e. higher relative risks for higher dose-sites, for younger ages at exposure and with longer time since diagnosis. Our dose-response analysis, however, was necessarily crude and sites were likely misclassified since we did not have individual treatment data on the radiotherapy fields used.

The main limitation of the SEER data, like any observational study of treatment effects, is the lack of treatment randomization and therefore the potential for confounding by indication. Confounding would occur if factors related to radiotherapy use were also related to the risk of second cancer. We used a number of approaches to try to minimize this and other potential biases. Firstly we excluded the first five years of follow-up from the analyses to reduce the potential impact of surveillance bias. We adjusted all analyses for likely confounding factors that were available including stage, age at diagnosis and year of diagnosis, attained calendar period and attained age. For some cancer sites receipt of radiotherapy rather than surgery may be associated with risk factors for second cancers like smoking if these risk factors are contra-indications for surgery. It was reassuring, therefore, that the results from the analysis restricted to patients who had had cancer related surgery were similar to those for all patients (+/–10%). In general though the relative risks were higher for second cancer sites that are smoking related.³⁸ Lack of data on smoking and other treatments including chemotherapy and hormonal therapy treatment means that it is likely that there is some residual confounding. The level of confounding may vary across the first cancer sites as the characteristics of the patients who do not receive radiotherapy vary, and could have resulted in either over-estimation or under-estimation of the risks related to radiotherapy.

Our results are for patients treated in the U.S. over the last 30 years, and radiotherapy techniques have changed during this time period. For most sites, however, we did not find strong evidence of trends in the risks over calendar time (Webtable 4). An unavoidable

limitation of studying the late effects of radiotherapy is that the most recent changes in practice cannot be studied. In particular, as all the patients were treated before 2003 the impact of the widespread introduction of intensity modulated radiotherapy (IMRT) could not be evaluated. There is concern that IMRT might actually increase second cancer risks due to the increased volume of tissue that receives low-level exposure,³⁹ and it will be important to study this question directly in the future. Nevertheless, we estimate that by fifteen years of follow-up the absolute risks for adults are typically only a few excess cancers per 1000 treated. Even if current practice substantially changed radiation doses to some organs, the general message that the second cancer risks from radiotherapy in adulthood are small, especially when compared with the treatment benefits, would remain the same.

In summary we found that a relatively small proportion of second cancers (<10%) in adult cancer survivors are likely to be related to radiotherapy, suggesting that most are due to other factors, such as lifestyle or genetics.

Research in Context

Systematic review—We searched Pubmed with key terms including “radiotherapy”, “secondary malignancy” and also terms for each of the fifteen 1st cancer sites of interest. We also searched reference lists in previous articles. All key articles are described in the discussion and articles that had published relative risks for all second cancers or all second solid cancers are shown in Webtable 5. Where more than one article was published from the same cohort we present results from the most recent publication. Only three of the previous studies had published estimates of the attributable risk for radiotherapy and only one had published estimates of the cumulative absolute risk. Our results were generally consistent with the existing evidence, where it was available. None of the previous studies had combined data from multiple first cancer sites.

Interpretation—Our results suggest that a relatively small proportion of second cancers (<10%) in adult cancer survivors are likely to be related to radiotherapy, suggesting that most are due to other factors, such as lifestyle or genetics. These findings can be used by physicians and patients to put the risk of radiation-related cancer into perspective when compared to the likely benefits of the treatment. Studies of the second cancer risks from newer radiotherapy treatments such as IMRT, however, are still required.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Relative Risk[‡] (RR) of second solid cancer for radiotherapy (RT) versus no radiotherapy (non-RT): according to first cancer site
[‡]RR adjusted for gender, attained age and attained calendar through the use of external rates (see methods for details) and additionally adjusted for stage, age at diagnosis and year of diagnosis through stratification.
Obs – observed. CNS=central nervous system.
*Second cancers of the same site were excluded as standard treatment usually involves surgical removal of the affected organ or because of second cancer coding rules (prostate).

Figure 2.

Relative risk[‡] (RR) of second solid cancers at high, medium and low dose sites[†] for radiotherapy versus no radiotherapy: according to first cancer site

[‡]Relative Risk adjusted for gender, attained age and attained calendar through the use of external rates (see methods for details) and additionally adjusted for stage, age at diagnosis and year of diagnosis through stratification.

[†]Sites included in each dose-group are listed in Webtable 1.

For rectum, cervix, endometrial, prostate and thyroid cancers second cancers of the same site were excluded as standard treatment usually involves surgical removal of the affected organ or because of second cancer coding rules (prostate).

CNS=central nervous system.

Table 1
Descriptive statistics of the five-year cancer survivors according to receipt of radiotherapy treatment (RT)

	RT		no RT		Follow-up		Age at diag		% RT by age at diagnosis (yrs)						% RT by year diagnosis			% RT by stage					
	n	%	n	%	RT	no RT	RT	no RT	Mean (yrs)	RT	no RT	<45	45-59	60-74	75-79	<1980	1980-9	1990+	Local	Regional	Distant		
1st cancer site	9714	58%	7012	42%	10.8	11.9	57	58				58%	62%	55%	46%	54%	53%	63%	33%	77%	81%		
Oral/pharynx (excl lip*)	1542	48%	1660	52%	12.3	15.0	55	51				44%	47%	53%	56%	32%	45%	56%	38%	69%	73%		
Salivary gland																							
Rectum**	9234	28%	24317	72%	10.6	12.1	61	63				39%	31%	24%	-	8%	23%	37%	15%	50%	42%		
Anus	1618	66%	836	34%	10.9	12.7	58	59				68%	65%	67%	62%	28%	62%	77%	62%	71%	77%		
Larynx	9131	74%	3214	26%	11.8	13.1	61	60				71%	73%	75%	77%	66%	72%	80%	74%	75%	73%		
Lung (non-small cell)#	7218	23%	23775	77%	9.5	11.0	61	62				27%	27%	21%	18%	20%	23%	25%	7%	46%	57%		
Soft tissue (non-limbs)	746	33%	1514	67%	12.0	13.8	51	51				32%	33%	34%	32%	21%	33%	36%	29%	45%	36%		
Female breast	90613	40%	137191	60%	11.0	13.2	57	59				42%	43%	37%	32%	21%	25%	52%	39%	40%	48%		
Cervix**	7779	40%	11494	60%	14.7	16.8	52	42				25%	53%	66%	-	49%	42%	34%	25%	85%	86%		
Endometrial**	19618	36%	34595	64%	14.8	14.1	62	60				24%	34%	39%	-	48%	39%	27%	32%	72%	61%		
Prostate†	76363	38%	123800	62%	9.4	10.1	68	66				-	28%	40%	43%	29%	37%	39%	-	42%	24%		
Testes (seminomas)	6430	79%	1712	21%	15.8	14.3	37	37				79%	80%	78%	70%	86%	82%	76%	82%	73%	39%		
Eye/orbit	556	26%	1581	74%	10.8	13.4	56	56				25%	28%	25%	22%	6%	22%	39%	26%	33%	41%		
Brain/CNS‡	4075	61%	2559	39%	12.1	12.3	40	42				64%	59%	50%	24%	71%	69%	55%	-	-	-		
Thyroid	10904	39%	16871	61%	12.7	16.3	44	44				40%	38%	38%	37%	14%	32%	49%	30%	54%	63%		

* Lip excluded as <20% of patients received radiotherapy (see methods for details).

** Age-groups 60-74 and 75+ yrs were combined due to small numbers.

44% of cancer staging is unknown.

† Local/regional stages combined.

‡ No stage data avail

Table 2

Relative risk (RR)[‡] of second solid cancer at high-dose sites for radiotherapy versus no radiotherapy: according to age at diagnosis of the first cancer and first cancer site

	Diagnosed <age 45		Diagnosed age 45–59		Diagnosed age 60–74		Diagnosed age 75+		p-trend
	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)	
1st cancer site									
Oral/pharynx (excl lip)		0.70 (0.49–0.99)	1.18 (1.03–1.35)	1.14 (0.99–1.33)	1.27 (0.63–2.58)	0.10			
Rectum*		1.09 (0.48–2.27)	1.00 (0.78–1.27)	1.19 (1.00–1.42)	1.61 (0.91–2.72)	0.14			
Larynx [#]		1.04 (0.46–2.57)	1.52 (1.07–2.21)	1.17 (0.76–1.83)	-	0.73			
Lung (non-small cell)		1.42 (0.93–2.12)	1.29 (1.11–1.50)	1.20 (1.03–1.38)	1.14 (0.58–2.11)	0.33			
Female breast		1.83 (1.46–2.29)	1.45 (1.29–1.62)	1.15 (1.03–1.28)	1.03 (0.63–1.66)	<0.0001			
Cervix (external beam) ^{**#}		3.25 (2.21–4.79)	1.48 (1.06–2.08)	1.15 (0.76–1.75)	-	0.00068			
Endometrium (external beam) [*]		3.25 (2.08–5.04)	1.65 (1.37–1.98)	1.72 (1.47–2.01)	0.92 (0.46–1.74)	0.036			
Prostate (external beam) ^{*†}		-	1.85 (1.53–2.22)	1.48 (1.38–1.58)	1.16 (0.96–1.14)	0.00070			
Thyroid ^{**#}		1.34 (0.69–2.52)	1.08 (0.58–1.93)	0.78 (0.39–1.47)	-	0.24			

RR[‡] – adjusted for gender, attained age and attained calendar through the use of external rates (see methods for details) and additionally adjusted for stage, age at diagnosis and year of diagnosis through stratification.

[#] Highest age-group of 60+ used due to small numbers.

^{*} Second cancers of the same site were excluded as standard treatment usually involves surgical removal of the affected organ or because of second cancer coding rules (prostate).

[†] No second cancers observed in the youngest age-group.

For endometrial and prostate cancer the group treated with external beam radiotherapy includes patients treated with external beam and brachytherapy.

Table 3

Relative risk (RR)[‡] of second solid cancer at high-dose sites for radiotherapy versus no radiotherapy: according to time since first cancer diagnosis (latency) and first cancer site

1st cancer site	Latency 5–9 yrs		Latency 10–14 yrs		Latency 15+ yrs	
	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)
Oral/pharynx (excl lip)	1.12	(0.99–1.27)	1.14	(0.95–1.38)	0.95	(0.74–1.22)
Rectum*	1.13	(0.94–1.35)	1.33	(1.03–1.70)	0.91	(0.64–1.27)
Larynx	1.57	(1.08–2.36)	1.04	(0.66–1.70)	1.29	(0.75–2.30)
Lung (non-small cell)	1.12	(0.98–1.27)	1.37	(1.12–1.65)	1.62	(1.23–2.09)
Female breast	1.17	(1.05–1.30)	1.42	(1.24–1.62)	1.56	(1.34–1.81)
Cervix (external beam)*	1.18	(0.79–1.75)	1.55	(1.00–2.40)	2.59	(1.84–3.68)
Endometrium (external beam)*	1.30	(1.08–1.56)	1.99	(1.60–2.47)	2.18	(1.78–2.65)
Prostate (external beam)*	1.39	(1.29–1.50)	1.59	(1.41–1.80)	1.91	(1.53–2.38)
Thyroid*	0.89	(0.49–1.55)	1.03	(0.47–2.14)	1.21	(0.64–2.17)

[‡] RR[‡] – adjusted for gender, attained age and attained calendar through the use of external rates (see methods for details) and additionally adjusted for stage, age at diagnosis and year of diagnosis through stratification.

* Second cancers of the same site were excluded as standard treatment usually involves surgical removal of the affected organ or because of second cancer coding rules (prostate). For endometrial and prostate cancer the group treated with external beam radiotherapy includes patients treated with external beam and brachytherapy.

Table 4

Estimated number of excess second solid cancers related to radiotherapy treatment[†] and attributable risk in those treated with radiotherapy: according to first cancer site

1st cancer site	Obs RT ^{**}	Persons	Excess cancers [†]		% Attributable risk	
			n	(95% CI)		(95% CI)
Oral/pharynx (excl lip)	3683	24880	182	(53–310)	5%	(1%–8%)
Salivary gland [*]	309	3007	37	(1–71)	12%	(0%–23%)
Rectum [*]	1568	21841	112	(41–184)	7%	(3%–12%)
Anus	323	3444	32	(–14–74)	10%	(–4%–23%)
Larynx	3583	17070	193	(32–350)	5%	(1%–10%)
Lung (non-small cell)	2395	51270	152	(82–223)	6%	(3%–9%)
Soft tissue (non-limbs)	120	1602	18	(–2–39)	15%	(–2%–32%)
Female breast	12450	150661	660	(454–866)	5%	(4%–7%)
Cervix [*]	1289	14685	214	(130–295)	17%	(10%–23%)
Endometrium [*]	3269	29338	286	(165–407)	9%	(5%–12%)
Prostate [*]	11292	128582	1131	(956–1307)	10%	(8%–12%)
Testes (seminomas)	628	7862	150	(56–233)	24%	(9%–37%)
Eye and orbit	112	1085	4	(–12–22)	4%	(–11%–20%)
Brain/CNS	314	13220	28	(–11–66)	9%	(–3%–21%)
Thyroid [*]	959	16934	67	(6–128)	7%	(1%–13%)
Total	42294	485481	3266	(2862–3670)	8%	(7%–9%)

RT – radiotherapy

^{**} In all patients (defined as 1+ year survivors)

[†] Estimated in 5+ year survivors calculated using the Poisson regression models in Table 2.

^{*} Second cancers of the same site were excluded as standard treatment usually involves surgical removal of the affected organ or because of second cancer coding rules (prostate).